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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,476	PIASIO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-21* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENTS

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 10/27/04, 11/08/04, 11/22/04, 03/23/05, 06/13/05 and 10/13/05 in response to the non-final Office Action mailed 07/27/04. Applicants have amended the specification.

Status of Claims

2) New claims 9-14 have been added via the amendment filed 11/22/04.

Claims 1-9 have been canceled via the amendment filed 03/23/05.

Claims 10-15 have been amended via the amendment filed 03/23/05.

Claims 10-15 have been canceled via the amendment filed 06/13/05.

New claims 16-21 have been added via the amendment filed 06/13/05.

Claims 16-21 are pending.

Claims 16-20, covering the elected subject matter, are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Moot

5) The objection to claim 5 made in paragraph 8(a) of the Office Action mailed 7/27/04 is moot in light of Applicants' cancellation of the claim.

6) The objection to claim 8 made in paragraph 8(b) of the Office Action mailed 7/27/04 is moot in light of Applicants' cancellation of the claim.

Objection(s) Withdrawn

7) The objection to the specification made in paragraph 3 of the Office Action mailed 7/27/04 is withdrawn based on Applicants' statement that they have not incorporated by reference the commonly

assigned co-pending application 09/518,165, but are relying upon it only as a prior filed co-pending application containing additional pertinent information.

Objection(s) Maintained

8) The objection to the specification made in paragraph 3 of the Office Action mailed 7/27/04 is maintained for reasons set forth therein.

Specification

9) The instant specification is objected for the following reason(s):

(a) The amendment introduced to the first full paragraph on page 4 of the instant specification via the amendments filed 10/27/04 and 11/08/04 by inserting the limitation 'which is incorporated herein by reference' and 'also' its parent application ... is objected to under 35 U.S.C. § 132, because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The current 'incorporation by reference' to two applications, 09/397,110 and its parent application 09/156,486, constitutes new matter. For the incorporation by reference to be effective as a proper safeguard against the omission of a portion of a prior application, the incorporation by reference statement must be included in the specification-as-filed, or transmittal letter-as-filed, or an amendment specifically referred to in an oath or declaration executing the application. An incorporation by reference statement added after an application's filing date is not effective because no new matter can be added to an application after its filing date. See 35 U.S.C § 132(a).

(b) The instant specification is objected to under 35 U.S.C. § 132, because it introduces new matter into the disclosure. The amendment introduced to the first paragraph at page 2 of the specification via the amendments filed 10/27/04 and 11/08/04 replaces the limitation 'pneumonic' with the limitation --other respiratory--. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The specification, as originally filed, did not equate the term 'pneumonic' diseases to 'other respiratory' diseases. Applicants are required to cancel the new matter in response to this Office Action.

Rejection(s) Moot

10) The rejection of claims 1-8 made in paragraph 5 of the Office Action mailed 07/27/04 under 35 U.S.C § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the

claims.

11) The rejection of claim 1 made in paragraph 7(a) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

12) The rejection of claim 1 made in paragraph 7(b) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

13) The rejection of claim 1 made in paragraph 7(c) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

14) The rejection of claim 1 made in paragraph 7(d) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

15) The rejection of claim 3 made in paragraph 7(e) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

16) The rejection of claims 4 and 7 made in paragraph 7(f) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

17) The rejection of claim 6 made in paragraph 7(g) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

18) The rejection of claim 8 made in paragraph 7(h) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

19) The rejection of claims 2-8 made in paragraph 7(i) of the Office Action mailed 07/27/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

Response to Applicants' Arguments

20) With regard to the lack of enablement rejection set forth at paragraph 5 of the Office Action mailed 07/27/04, Applicants submit the following arguments. Applicants state that they have not incorporated by reference the commonly assigned, copending U.S. patent application 09/518,165 but are relying upon it only as a prior filed co-pending application containing additional pertinent information. Applicants submit that the present application as filed clearly referred to application serial no. 09/397,110 at page 6, last line and, in its last paragraph, page 10, pointed to the fact that all the examples herein employ antibodies to *Streptococcus pneumoniae* treated as described therein in detail, to render them specific to the C-polysaccharide cell wall antigen present in all serogroups of *S. pneumoniae*, and contains a wholly enabling disclosure which complies fully with 35 U.S.C. § 112. Applicants contend that since the correct application was referred to at least once in the application as filed, a person of ordinary skill in the art, recognizing 09/399,710 to be an incorrect number would have consulted application serial no. 09/397,110 and almost instantly have recognized it to be the copending, commonly assigned application intended to be referred to throughout, and have understood that its disclosure of 'how to obtain purified antigen-specific antibodies capable of recognizing the C-polysaccharide antigen of *S. pneumoniae* with exceptional specificity and sensitivity' is all that is needed to complete the explanation herein of exactly how to achieve the results specifically disclosed herein, in connection with modifying a bioassay for *S. pneumoniae* to reduce the incidence of false positive tests for infection obtained on samples of bodily fluid (such as urine) obtained from nasopharyngeally colonized but otherwise healthy children under the age of about 12.

Applicants' arguments have been carefully considered, but are not persuasive.

With regard to Applicants' statement that they are relying on the co-pending U.S. patent application 09/518,165 only as prior filed application that contains additional pertinent information, the following should be noted. The claims under examination in application 09/518,165 are drawn to a method of obtaining antigen-specific antibodies to a target bacterial carbohydrate antigen from Gram negative bacteria. It must be noted that the disclosure of the issued application 09/397,110 is limited to obtaining antibodies to the cell wall C-polysaccharide antigen of only *Streptococcus pneumoniae* bacterium. Therefore, it appears that in order to practice the subject matter claimed at least in instant claims 16, 17 and 19, one of skill in the art has to rely on the disclosure of the co-pending US patent application serial no. 09/518,165 as this application appears to be related to a method of obtaining

target carbohydrate antigen-specific antibodies capable of recognizing the target carbohydrate antigen of non-*S. pneumoniae* bacteria, including *Haemophilus influenzae* type b, *Legionella pneumophila*, *Staphylococcus aureus*, *Moraxella catarrhalis* etc. Obtaining antibodies of 'exceptional specificity and sensitivity' that recognize a target carbohydrate antigen of non-*S. pneumoniae* bacteria, including *Haemophilus influenzae* type b, *Legionella pneumophila*, *Staphylococcus aureus*, *Moraxella catarrhalis,* is associated with high unpredictability. More than half a dozen publications cited below have documented this recognized unpredictability factor and/or lack of success in using the anti-carbohydrate antigen antibodies to discriminate between bacterial infection and nasopharyngeal colonization. The claims of the co-pending US patent application 09/518,165 however stand rejected currently under 35 U.S.C § 112, first paragraph as being non-enabled.

Applicants' amendment to the specification to correct the application number from the incorrect 09/399,710 to the correct 09/397,110 has been noted. However, this correction of the application number alone is insufficient to overcome the lack of enablement rejection of record. The current incorporation by reference of application 09/397,110 and its parent application 09/156,486, is new matter. See paragraph 9(a) above. The following should be noted with regard to Applicants' statement that the disclosure from application 09/397,110 of 'how to obtain purified antigen-specific antibodies capable of recognizing the C-polysaccharide antigen of *S. pneumoniae* with exceptional specificity and sensitivity' is all that is needed to complete the explanation herein of exactly how to achieve the results specifically disclosed herein, in connection with modifying a bioassay for *S. pneumoniae* to reduce the incidence of false positive tests for infection obtained on samples of bodily fluid (such as urine) obtained from nasopharyngeally colonized but otherwise healthy children under the age of about 12. The essential material from application 09/397,110 is not described in the instant application in sufficient detail for one of skill in the art to practice the claimed improved invention. In addition to this, there is growing pre-filing and post-filing evidence in the art documenting the lack of success of the invention for the intended purpose. As set forth at paragraph 5 of the Office Action mailed 07/27/04, the state of the art reflects unpredictability and/or lack of success with Binax NOW bioassay for serologically distinguishing children with pneumococcal pneumonia from those who are merely colonized. See the teachings of Dowell *et al.* (*Clin. Infect. Dis.* 32: 824-825, 2001, already of record) and Adegbola *et al.* (*Pediatr. Infect. Dis. J.* 20: 718-719, July 2001, already of record) therein. See also the teachings of Navarro *et al.* 2004, Nariai *et al.* 2004, Dominguez *et al.* 2003, Hamer *et al.* 2002,

and Magentie *et al.* 2003 in paragraph 21 below. Contrary to Applicants' assertion, the examples from application 09/397,110, now US patent 6,824,997, employ antibodies to the C-polysaccharide cell wall antigen of *Streptococcus pneumoniae* that appear to be non-distinguishing of *S. pneumoniae* infection and nasopharyngeal colonization by *S. pneumoniae,* and therefore do not provide a wholly enabling disclosure for the instant claims under 35 U.S.C. § 112, first paragraph. On page 9 of their response filed 10/27/04, Applicants state that Dowell, and Adegbola *et al.* describe test results obtained with the NOW® test *prior to* the undertaking of the instant work. However, numerous published articles from the art, including pre-filing and post-filing articles, establish that the purified antigen-specific antibodies recognizing the C-polysaccharide antigen of *S. pneumoniae* are **not** of 'exceptional specificity and sensitivity'. See paragraph 21 below.

Rejection(s) based on Applicants' Amendment

Applicants are asked to note the new rejection(s) set forth below. The new rejections are necessitated by Applicants' amendments to the claims or submission of new claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

21) Claim 19 and those dependent therefrom are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 19 includes the limitations: 'sample introduction end' and 'the end of said strip remote from its sample introduction end'. However, there appears to be no descriptive support in the specification, as originally filed, for these new limitations. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph (Lack of Enablement)

22) Claims 16-20 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instant specification indicates that the claimed invention is obtained by modifying the ICT NOW® bioassay. For example, the 'Detailed Description of the Invention' on pages 7 and 10 of the instant specification refers to the US patent application, 09/397,110, now US patent 6,824,997. The sentence in the first paragraph of page 8 of the specification states the following:

> The modification disclosed herein of the NOW® test disclosed and claimed in U.S. Serial No. 09/397,110, now U.S. Patent 6,824,997 render the test as so modified highly useful in enabling physicians to make rapid, accurate diagnosis of pneumococcal pneumonia and/or otitis media caused by *Streptococcus pneumoniae* in children, which diagnoses are based on the modified test results combined with clinical observations of the individual patients.

Applicants did not incorporate by reference the commonly assigned U.S. patent application serial no. 09/397, 110 in the instant specification, *as originally filed*, but only cited it as a prior filed, co-pending application containing pertinent information. The specification further refers to another co-pending application, 09/518,165. The second full paragraph on page 5 of the specification states the following:

> Copending, commonly assigned U.S. application Serial No. 09/518,165 filed March 1, 2002, describes and claims rapid immunochromatographic tests for detecting bacterial carbohydrate antigens in human bodily fluids, including urine.

The second full sentence on page 8 of the specification states the following:

> Analogous modifications of the tests covered in U.S. Serial No. 09/518,165 render those tests as so modified very useful in enabling physicians to make rapid, accurate diagnoses of pneumonic diseases and otitis media of other bacterial origin in children, by combining the modified test results with clinical observation of individual child patients.

Neither of these applications was incorporated by reference into the specification *at the time of filing.* The instant application is not related to these 'commonly assigned' co-pending applications in terms of

priority or continuity. Page 8 of the instant specification states the following: 'a brief summary of the bioassay format described in both of the prior co-pending applications is provided'. The two applications are stated to provide a purification process for an essentially protein-free carbohydrate antigen characteristic of the bacteria. The paragraph bridging pages 8 and 9 of the specification provides a brief description of the disclosure of the co-pending applications. This brief description, however, is insufficient for one of skill in the art to practice the instant invention as claimed. The first sentence on page 11 of the specification states the following:

> In all of these Examples, test strips were prepared as described in earlier filed, copending Serial No. Application 09/397,110, now U.S. Patent 6,824,997 using antibodies to *Streptococcus pneumoniae* that has been purified and rendered antigen-specific as described in that application.

The disclosure of the application 09/397,110, does not provide enablement for the instantly claimed invention. The first full paragraph on page 4 of the instant specification states that the application 09/397,110 describes the NOW® bioassay. On page 7 of the response filed 10/27/04, Applicants state that the disclosure of application 09/397,110 of how to obtain purified antigen-specific antibodies capable of recognizing the C-polysaccharide antigen of *S. pneumoniae* 'with exceptional specificity and sensitivity is all that is needed to complete the explanation herein of exactly how to achieve the results specifically disclosed herein, in connection with modifying a bioassay for *S. pneumoniae* ...'. However, an increasing number of pre-filing and post-filing references continue to document that the antibodies to *Streptococcus pneumoniae* that have been purified and rendered antigen-specific as used in Binax NOW® bioassay (i.e., the one described in application 09/397,110) have proven to be non-specific, non-discriminating, and have given an unacceptable level of false-positive results in children who were not infected by *Streptococcus pneumoniae*, but were nasopharyngeally colonized. Clearly, the state of the art reflects unpredictability and the lack of success with Binax NOW® bioassay for serologically distinguishing children with pneumococcal pneumonia from those who are merely colonized. For instance:

(A) Dowell *et al.* (*Clin. Infect. Dis.* 32: 824-825, 2001, already of record) taught that the test was significantly more likely to be positive among children who were nasopharyngeal carriers of pneumococci (see abstract; Table 1; and page 824). More than half of the patients (> 50%) who did not have pneumonia but who had pneumococci in their nasopharynx had a positive result of the urine antigen detection test (see paragraph bridging 824 and 825).

(B) Similarly, Adegbola *et al.* (*Pediatr. Infect. Dis. J.* 20: 718-719, July 2001, already of record) stated the following with regard to the use of Binax NOW® test (see page 719):

> ..... The detection of urinary antigen in more than one-half of the children colonized by *S. pneumoniae* indicates that a positive result from this test does not necessarily imply active disease in children. Thus when used in a community with high pneumococcal carriage, a positive result from Binax NOW test must be interpreted with caution. The two "false positive" tests in our study may indeed have been true positives because the presence of pneumococcal antigen resulting from colonization is intermittent and pneumococcal antigen could be excreted in urine after the disappearance of *S. pneumoniae* from the nasopharynx.
>
> ..... Binax NOW test would **likely be of limited value** for detection of childhood pneumococcal pneumonia in our study population. In a recent study of the etiology of pneumonia in Beijing, China, the Binax NOW test was no more likely to be positive among children with radiographically confirmed pneumonia than among control children, and it was **more likely to be positive** among children who were colonized by *S. pneumoniae*. The test may also be **of limited value in the diagnosis of adult pneumonia** because of the relatively high carriage rates of *S. pneumoniae* in Gambian adults. ..... There was **no correlation** between the magnitude of nasopharyngeal carriage and the intensity of the color line in positive tests. [Emphasis added].

Adegbola *et al.* expressly stated that the Binax NOW *Streptococcus pneumoniae* urinary antigen test had a positive predictive value of 96% for nasopharyngeal carriage in children and a negative predictive value of 22% (see abstract). Adegbola *et al.* concluded that the Binax NOW *Streptococcus pneumoniae* urinary antigen test 'is not useful for predicting etiology of disease in populations with a high rate of nasopharyngeal carriage of pneumococci' (see abstract).

(C) Furthermore, Navarro *et al.* (*J. Clin. Microbiol.* 42: 4853-4855, 2004, abstract) performed the Binax NOW immunochromatographic test (ICT) for detecting *Streptococcus pneumoniae* antigen in urine specimens from children presenting underlying pulmonary diseases with no recent penumococcal infection and concluded that the Binax NOW ICT assay 'is **unlikely** to be useful for **discriminating** between children with and without pneumococcal pneumonia' [Emphasis added]. See abstract.

(D) Additionally, Nariai *et al.* (*Kansenshogaku Zasshi* 78: 18-21, January 2004, abstract) evaluated *Streptococcus pneumoniae* urinary antigen test in healthy children with nasopharyngeal pneumococcal carriage and found that 58.3% of the children with pneumococcal carriage and 27.3% of non-carriers has false-positive test results. Nariai *et al.* concluded that the 'test is not likely to be useful for diagnosing the etiology of childhood acute pneumococcal pneumonia' (see abstract).

(E) Dominguez *et al.* (*J. Clin. Microbiol.* 41: 2161-2163, May 2003, abstract) evaluated the usefulness of urinary antigen detection by the ICT assay for diagnosis of pneumococcal pneumonia in children and concluded that the test is a 'nonspecific' test for the diagnosis of pneumococcal

pneumonia in children (see abstract).

(F) Magentie *et al.* (*Ann. Biol. Clin.* 61: 106-109, Jan-Feb 2003, abstract) evaluated the Binax NOW *Streptococcus pneumoniae* urinary antigen test in urine samples from children and adults and concluded that the 'sensitivity and specificity' of the assay 'were lower than those announced by the manufacturer' (see abstract).

(G) Hamer *et al.* (*Clin. Infect. Dis.* 61: 1025-1028, April 2002) assessed the Binax NOW *Streptococcus pneumoniae* urinary antigen test in children with nasopharyngeal pneumococcal carriage and concluded as follows (see first paragraph under 'Discussion'):

> ..... rates of positive urinary antigen test results varied significantly according to the nasal colonization status of the patient. We suspect that these positive test results are due to the detection of pneumococcal antigen that originates from pneumococci colonizing the upper airways.

Hamer *et al.* further teach the following (see last two paragraphs under 'Discussion'):

> One potential shortcoming of our study was the failure to identify children with recent but resolving acute respiratory infections. Because pneumococcal antigens are shed for weeks after pneumonia resolves [3], recent but resolved infections might explain the false-positive urinary antigen test results for children who did not have carriage.
>
> On the basis of our results and the results of the studies from China and The Gambia [6,8], it appears that the Binax NOW *S. pneumoniae* urinary antigen test should be used with caution for the detection of pneumococcal pneumonia or bacteremia in young children, especially in developing countries where nasopharyngeal colonization rates are high.

In addition to this mounting evidence, the state of the art has documented the potential reason for the non-specificity of the anti-carbohydrate antibodies used in Binax NOW assay. The non-specificity of the antibodies is indicated to be due to their potential cross-reaction with antigens from other species of streptococcus other than *Streptococcus pneumoniae,* such as, *Streptococcus mitis* and *Streptococcus oralis.* See the sentence bridging the two columns on page 1027 of Hamer *et al.* (*Clin. Infect. Dis.* 34: 1025-1028, 2002).

The other co-pending U.S. patent application cited by Applicants in the instant specification is 09/518,165, which appears to disclose subject matter that is very relevant to the instantly claimed invention. The second full paragraph on page 5 of the specification states as follows:

> Copending, commonly assigned U.S. application Serial No. 09/518,165 filed March 1, 2002, describes and claims rapid immunochromatographic tests for detecting bacterial carbohydrate antigens in human bodily fluids, including urine.

The first full sentence on page 8 of the specification states the following:

> Analogous modifications of the tests covered in U.S. Serial No. 09/518,165 render those tests as so modified very useful in enabling physicians to make rapid, accurate diagnoses of pneumonic diseases and otitis media of

> other bacterial origin in children, by combining the modified test results with clinical observation of individual child patients.

The claims of the co-pending application 09/518,165 however stand rejected currently due to the lack of enabling disclosure. In order to make the required modifications to the tests described in the examples of the instant application, i.e., to practice the instant invention, one has to know of the bioassay format described in the recited co-pending patent application, 09/518,165. MPEP requires that an application *as filed* must be complete in itself in order to comply with 35 U.S.C. § 112. The disclosure of the patent application SN 09/397,110 does not provide enabling disclosure on the bioassay format, such that it can be modified as described in the examples of the instant application, to produce the instantly claimed invention. In other words, one cannot modify a bioassay: (a) which is not clearly, completely, and precisely described in the instant application; and (b) which has been repeatedly shown by at least seven groups of those of skill in the art to be non-specific or non-discriminating of pneumococcal infection and pneumococcal colonization in children. With the above-cited pre-filing and post-filing facts, being reflective of the state of the art, one of skill in the art would look into Applicants' specification for clear, complete, precise direction and guidance to practice the invention as claimed, which in the instant application is lacking. It is important that the essential material that renders the claimed invention novel must be described in the instant specification in full detail such that one of skill in the art can practice the invention without undue experimentation. Specific operative embodiments must be precisely and fully described. An incomplete disclosure or description does not enable one of skill in the art to which the invention pertains to make and use the invention as of its effective filing date.

Furthermore, instant claim 16 is very broad. Claims 16-18 are not limited to an ICT assay. The term 'target carbohydrate antigen that is characteristic of a bacterium causative of human ear and respiratory tract infections' encompasses a lipopolysaccharide antigen, capsular polysaccharide antigen, cell wall carbohydrate antigen etc. The target carbohydrate antigen can be isolated, or non-isolated as is present on the surface of the whole bacterium. The recited bacterium encompasses aerobic and anaerobic bacteria as well as Gram positive and Gram negative bacteria. In order to use 'antibodies to said carbohydrate antigen' in each generic bioassay, one has to produce antibodies to the antigen that is characteristic of any of these bacteria. The claimed bioassay improvement is applicable for detection of any bacterial agent causative of human ear and respiratory tract infections, which also

colonizes the nasopharynx areas of children of the recited age. The state of the art as explained above has reasonably documented that the antibodies raised to the carbohydrate antigen of at least one such bacterium were not of 'exceptional specificity and sensitivity' as has been asserted and would not provide an acceptable bioassay specificity as to distinguish children with ear and respiratory infections from otherwise healthy children with nasopharyngeal colonization. Clearly, undue experimentation would have been required by one of skill in the art at the time of the invention due to the lack of direction and specific guidance, the lack of enabling disclosure, the unpredictability and lack of success as indicated by the state of the art, the breadth of the claims, and the quantity of experimentation necessary.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

23) Claims 16-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Instant claims are very poorly written and include limitations that are inconsistent in scope, that lack proper antecedent basis, and/or that have improper antecedent basis, some of which are identified below.

(a) Claims 17-20 are indefinite and/or lack proper antecedence in the limitation: 'A bioassay according to Claim ...'. For proper antecedence, it is suggested that Applicants replace the limitation with --The bioassay according to claim ...--.

(b) Claim 17 is vague and indefinite in the limitation: 'Claim 16 wherein the target antigen is a carbohydrate antigen', because claim 16 already includes the recitation 'a target carbohydrate antigen ..... *Staphylococcus aureus*'. For the purpose of distinctly claiming the instant invention and/or in order to be properly further limiting, it is suggested that Applicants replace the limitation with --claim 16 wherein the bacterium is selected from the group consisting of *Streptococcus pneumoniae* ..... *Staphylococcus aureus*'--.

(c) Claim 18 is vague and indefinite in the limitation: 'Claim 16 wherein the target antigen is', because claim 16 already includes the recitation a 'target carbohydrate antigen'. For the purpose of distinctly claiming the instant invention, it is suggested that Applicants replace the limitation with --claim 16 wherein the target carbohydrate antigen is--.

(d) Claim 19 is vague, indefinite and confusing in the limitation 'liquid sample' (see line 4),

'the sample' (see lines 6 and 7) and 'sample' (see line 9), because it is unclear how one differs from the other in terms of scope. Claim 19 depends from claim 16, which recites that the bioassay is for the detection in human 'bodily fluids'. There is no recitation of any 'liquid sample' or 'sample' in claim 16.

(e) Claim 19 is vague, indefinite and confusing in the limitation: 'enabling formation of tagged-antigen conjugates if target antigen is present', because it is unclear how 'conjugates' (having covalent bonds) can be formed between movable deposits of tagged antibodies and the target antigen. Does this mean that these conjugates have covalent bonds between the antigen and antibody elements? Does it mean that the target carbohydrate antigen in the bodily fluid is activated such that it forms a covalent conjugate on contact with the tagged antibodies?

(f) Claim 19 is vague, indefinite and confusing in the inconsistent limitations: 'the target carbohydrate antigen' (see line 2); '-antigen' (see lines 6 and 9); 'target antigen' (see line 6); and 'the target antigen' (see line 7). How one differs from the other in terms of scope is not clear.

(g) Claim 19 is vague, indefinite and confusing in the limitation: 'its sample introduction end' (see lines 8 and 9). It is unclear whether this 'sample introduction end' is different from the one recited in line 3 of the claim.

(h) Claim 19 is vague in the limitation: 'bioassay according to Claim 16 conducted on'. For clarity, it is suggested that Applicants replace the limitation with --bioassay according to claim 16 wherein said bioassay is conducted on--.

(i) Claim 20 is indefinite and confusing in the limitation: 'the antibodies' (see line 1) and 'said antibodies' (see lines 7 and 8), because it is unclear where does the antecedence come from. Claim 20 depends from claim 19, which recites 'tagged antibodies' in line 2 and 'antibodies' in line 7.

(j) Claim 20 is indefinite and has improper antecedent basis in the limitation: 'the tag material' (see line 3). Claim 20 depends from claim 19 which does not recite a 'tag material'. For proper antecedent basis, it is suggested that Applicants replace the limitation with --the tag--.

(k) Claim 20 is further vague and confusing in the limitation 'antibodies' (see line 9). Are these antibodies same as or different from those recited in line 3 of the claim? What are these antibodies specific to is not clear.

(l) Claim 20 is also vague and confusing in the limitation 'tagged antibodies' (see line 7). Are these 'tagged antibodies' different from the ones recited in line 2 of claim 19, from which claim 20

depends.

(m) Claim 20 is vague and indefinite in the limitation 'having an optical density of 1.5', because it is unclear at what wavelength is this optical density measured.

(n) Claim 20 appears to lack proper antecedent basis in the limitation 'strip' (see last part of line 10). Is this strip different from the earlier recited 'the strip' (see first half of line 10)?

(o) Claims 17-20, which depend directly or indirectly from claim 16, are also rejected as being vague and indefinite because of the indefiniteness identified above in the base claim.

Objection(s)

24) Claim 20 is objected to for placing a period '.' following the limitations 'mg', 'ml' in line 9 and following the limitation 'ml' and 'mm' in line 10 of claim 20. It is suggested that Applicants remove the period from these locations.

Relevant Art

25) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Moore *et al.* (US 6,824,997) disclosed the NOW Binax ICT device and assay for detecting the presence of the cell wall C-polysaccharide antigen of *Streptococcus pneumoniae* in a liquid sample. See entire document.

Remarks

26) Claims 16-20 stand rejected.

27) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

29) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

December, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER